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Immunosuppression reduction when administering a booster dose of the BNT162b2 mRNA SARS-CoV-2 vaccine in kidney transplant recipients without adequate humoral response following two vaccine doses: protocol for a randomised controlled trial (BECAME study)

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ABSTRACT

Introduction Inadequate antibody response to mRNA SARS-CoV-2 vaccination has been described among kidney transplant recipients. Immunosuppression level and specifically, use of antimetabolite in the maintenance immunosuppressive regimen, are associated with inadequate response. In light of the severe consequences of COVID-19 in solid organ transplant recipients, we believe it is justified to examine new vaccination strategies in these patients.

Methods and analysis BECAME is a single-centre, open-label, investigator-initiated randomised controlled, superiority trial, aiming to compare immunosuppression reduction combined with a third BNT162b2 vaccine dose versus third dose alone. The primary outcome will be seropositivity rate against SARS-CoV-2. A sample size of 154 patients was calculated for the seropositivity endpoint assuming 25% seropositivity in the control group and 50% in the intervention group. A sample of participants per arm will be also tested for T-cell response. We also plan to perform a prospective observational study, evaluating seropositivity among ~350 kidney transplant recipients consenting to receive a third vaccine dose, who are not eligible for the randomised controlled trial.

Ethics and dissemination The trial is approved by local ethics committee of Rabin Medical Center (RMC-0192-21). All participants will be required to provide written informed consent. Results of this trial will be published; trial data will be available. Protocol amendments will be submitted to the local ethics committee.

Trail registration number NCT04961229.

Strengths and limitations of this study

- This randomised controlled trial addresses a question of crucial importance for organ transplant recipients during the COVID-19 pandemic.
- Allocation concealment will reduce the risk of bias, although blinding will not be possible.
- Antibody level measures for all participants at several timepoints, and partial sampling for T-cell response will provide an overview on protectivity of vaccine.
- Currently, no neutralising antibody testing is planned, limiting the evaluation of protective effect of the vaccine.
- The study is open label; however, the primary outcome is an objective laboratory test result.

INTRODUCTION

COVID-19 outbreak has great impact on solid organ transplant recipients. Mortality rates among kidney transplant recipients have been reported between 13% and 50%, with high rates of complications, including acute kidney injury (AKI) in 30%–89% of hospitalised patients.[1] Severe consequences of COVID-19 were also demonstrated among vaccinated kidney transplant recipient who were infected with SARS-CoV-2, with considerable mortality.[2]

The Pfizer mRNA-based BNT162b2 vaccine, the first vaccine approved by the FDA against SARS-CoV-2 infection, has been delivered to over 5 million people in Israel since December 2020. Immunocompromised patients were excluded from the phase III trial evaluating this vaccine, and thus, the efficacy and safety of the vaccine in this patient population are currently not well studied.[3] A large study from Israel has

validated the effectiveness of this vaccine in the general population[4]; however, the number of vaccinated solid organ transplant recipients in this cohort (n=435) was too small for performing evaluation of vaccine effectiveness for this sub-group.[5]

The American Society of Transplantation and other transplantation societies in the world have recommended vaccinating transplant candidates and recipients against SARS-CoV-2 despite lack of data regarding efficacy in these populations, based on encouraging clinical results in other populations.[6]

Early phase I/II studies showed that BNT162b2 elicited strong antibody response in healthy adults. The titre of the neutralising antibodies increased with dose and also increased after the second injection in comparison with the first.[7 8] High rates of antibody response to two doses of the vaccine were also documented in healthy population, accompanied by a distinct Th1 type T-cell response.[9] While the role of neutralising antibodies in protection from SARS-CoV-2 was demonstrated, it is expected that a steady T-cell response has a central role against SARS-CoV-2 infection.[10] Solid organ recipients are expected to gain lower immune response to vaccinations with varying effectiveness between different vaccines and different transplanted organ populations.[11] Broad impairments in both humoral and cellular response to mRNA vaccines have been reported in kidney transplant recipients. Several studies from Israel demonstrated low rates of antibody response to the BNT162b2 vaccine among solid organ transplant recipients, including 36% seropositivity among 308 kidney transplant recipients 2–4 weeks after the second vaccine dose[12]; 47% seropositivity among 80 liver transplant recipients[13]; 49% among 37 heart transplant recipients[14]; and 18% among 168 lung transplant recipients.[15] Most demonstrated an association between mycophenolic acid dose and calcineurin inhibitor blood levels and antibody response. A large study evaluating response to either BNT162b2 vaccine or the mRNA-1273 (Moderna) vaccine among 658 organ transplant recipients also demonstrated low seropositivity rates of 54% a median of 29 days after two vaccine doses.[16] In addition, diminished generation of plasmablasts and memory B cells in response to mRNA vaccine among kidney transplant recipients were reported.[17] Impairments in T-cell response were also described, with high rates of spike-specific T helper cell response, however reduced magnitude of response, as well as limited effector cytokine production.[18 19] Recent studies demonstrate improve humoral and cellular responses following third booster mRNA vaccine dose among transplant recipients. Yet, a considerable portion of these patients remained seronegative.[20–22] We plan a randomised controlled trial aiming to evaluate whether a third booster dose of mRNA SARS-CoV-2 vaccine BNT162b2, with or without immunosuppression reduction, improves the humoral response in kidney transplant recipients.

METHODS AND ANALYSIS

Study hypothesis and aims

We aim to evaluate the effect of a third mRNA vaccine dose with and without immunosuppression reduction on rates of seropositivity among kidney transplant recipients. We hypothesise that immunosuppression reduction combined with a third dose will demonstrate superiority over a third dose alone in terms of seropositivity rates.

Study design

The study is a single-centre, randomised controlled, superiority, open-label trial, with an observational cohort as below:

Randomised controlled trial (two arms)

Third dose of BNT162b2 vaccine with or without reduction of mycophenolic acid dose (see below).

Observational arm

A third vaccine dose with no change in immunosuppression for patients that are excluded from the randomised trial (see exclusion criteria).

Setting

The study will be conducted at Rabin Medical Center in Israel, in the transplantation follow-up clinic.

Study population

We will include in both the RCT and observational study adult (age ≥18 years) kidney transplant recipients who received two doses of BNT162b2 vaccine at least 3 weeks prior to enrolment, and were seronegative (IgG against the spike protein of SARS-CoV-2 below 50 AU/mL) at least 2 weeks after the second vaccine dose.

Additional inclusion criteria for the RCT

Recipients treated with three anti-rejection medications including prednisone, tacrolimus, mycophenolate mofetil or mycophenolic acid.

Patients with any dosage of mycophenolic acid, mycophenolate mofetil and prednisone will be eligible for inclusion. Regarding tacrolimus, trough blood levels 5–10 nGr/mL will be required for inclusion. Lower or higher doses will have to be adjusted before re-considering for inclusion.

Exclusion criteria for both RCT and observational part

- Past infection with SARS-CoV-2.
- Pregnancy.
- Age below 18 years.
- Active infection.

Additional exclusion criteria for RCT only

Recipients at a high risk for acute or chronic humoral rejection including:

- Recipients with positive panel-reactive antibody (any positive value) at any time before or after transplantation.
- Recipients that had an acute rejection in the last year.
- Recipients less than 6 months after transplantation.
- Recipients that are considered at high risk for rejection according to the primary care nephrologist.
- Recipients taking less than three anti-rejection medications.

- Recipients currently treated with mTOR inhibitors (everolimus, sirolimus) and/or azathioprine.
- Recipients treated with plasmapheresis in the previous 3 months.
- Recipients treated with eculizumab in the last year.
- Recipient treated with IVIG in the previous 3 months.
- Recipient treated with rituximab in the previous 6 months.

Patients can withdraw from the study at any time.

Patient randomisation

Patients will be randomised to immunosuppression reduction versus no immunosuppression reduction in a 1:1 ratio. Randomisation will be performed using a computer-generated list of random numbers that will be allocated centrally through a website.

Interventions

All recipients more than 6 months post-transplantation and at least 3 weeks following second vaccine dose will be approached and invited to a first study visit (for trial flow see online supplemental appendix 1 part A).

At first visit

- Signed informed consent will be obtained from participants willing to participate by study investigators who routinely work in the transplantation clinic.
- Anti-spike antibody response will be assessed using SARS-CoV-2 IgG II Quant (Abbott) assay.[23] Participants who have a documented seronegative test in the last 6 weeks will not be tested again.
- Tacrolimus levels will be obtained.

Participants will be invited for an additional visit once negative serology result will be reported, within 7 days of test collection. At this second visit, all participants who gave informed consent to participate in either the prospective non-randomised study or RCT will receive a single vaccine dose.

In addition, participants in the RCT will be randomised into two groups:

1. Third booster dose of BNT162b2 (one standard dose) with no change in immunosuppression protocol.
2. Third booster dose of BNT162b2 (one standard dose) with immunosuppression reduction according to protocol (mycophenolic temporary cessation 4 days before (five half-lives) and 1 week (expected antibody response) after vaccination (to allow for antibody response).

Patients who will test seronegative will be informed by the study coordinator by phone in which study arm they will be participating and receive instructions for immunosuppression reduction both during the phone call and by written instructions provided to each patient during the first visit (see online supplemental appendix 1 part B). Participants in the observational study will receive a third vaccine standard dose, without any change in immunosuppression (beyond routine care).

For all groups

- Antibodies titre against spike protein will be evaluated at 2 weeks and 3, 6 and 12 months after the third vaccine dose.
- T-cell response will be evaluated for a small, randomly selected, subset of patients in each group (estimated 20 patients per arm) before booster dose, at 2 weeks after booster dose and at 3 months. For T-cell response quantification, peripheral blood mononuclear cell will be stimulated for 24 hours with spike protein and secreted interferon-gamma (IFNg) will be measured by ELISA (using the SARS-CoV-2 IFNg release assay EUROIMMUN, Lübeck, Germany).[24]
- Follow-up for adverse events, rejection or SARS-CoV-2 infection will be performed at 2 weeks and at 3, 6 and 12 months post-third vaccination dose.

Outcomes

The primary outcome of both RCT and observational study will be humoral response against SARS-CoV-2, defined as anti-spike protein titre above 50 AU/mL at 2 weeks post-vaccination.

Secondary outcomes

- Humoral response against SARS-CoV-2 at 3, 6 and 12 months post-vaccination.
- Humoral response of >4160 AU/mL, corresponding with antibody neutralisation[25 26]
- Log-transformed titre of anti-S protein at 2 weeks and 3, 6 and 12 months.
- Log-transformed change in anti-spike protein titre at 2 weeks and 3, 6 and 12 months.
- Adverse events to booster dose at 2 weeks post-vaccine. Severity of adverse events will be assessed using CTCAE v4.0 criteria.
- Acute rejection of the allograft at 2 weeks, 3, 6 and 12 months (documented by biopsy).
- SARS-CoV-2 infection during the follow-up period (until 12 months following vaccine).
- Other viral reactivation during the follow-up period (VZV, CMV), tested according to clinical suspicion.
- Number of hospitalisations until 12 months.

Due to technical limitations, we do not plan biobanking in this study.

Monitoring outcomes

Participants in both RCT and observational study will be invited for a clinic visit at 2 weeks, 3, 6 and 12 months at the post-transplant follow-up clinic at Rabin Medical Center. During their visit, they will be questioned for adverse events (see online supplemental appendix 1 part C for questionnaire); blood and urine tests will be checked as in the usual post-transplant follow-ups for creatinine levels, any increase in creatinine of more than 20% will be promptly followed by kidney biopsy (after excluding other reasons), urine protein or microalbumin, tacrolimus levels and anti-spike protein antibodies. Data will be entered to the REDCap software, and the primary

investigator will be responsible to check for timely data entry, missing data and suspected faulty data.

Predefined subgroup analysis

Recipients 65 years and older.

Sample size

The trial is designed to demonstrate superiority of immunosuppression reduction in terms of seropositivity rates. For the seropositivity endpoint, we calculated a sample size of 77 participants per arm, assuming a 25% seropositivity rate in the control group and 50% in the intervention group,[22] with a one-sided hypothesis with 2.5% α-risk and 90% power.

For the observational study, we assume ~350 participants.

Stopping rules

We plan to assess for acute rejection episodes following first 20 participants allocated to the immunosuppression reduction arm. If an acute rejection episode will be demonstrated within 2 weeks of follow-up from the booster dose—the study will be terminated. Acute rejection will be defined as a 20% increase from baseline creatinine with no other plausible explanation. Need for histological proof of rejection will be discussed case by case by an independent safety monitoring committee. In addition, interim analyses will be performed after the recruitment of each 50 participants. At each analysis, rejection episodes will be evaluated and rates of seropositivity will be assessed. An independent safety monitoring committee of three nephrologists or ID physicians, specialist in managing transplant patients, will meet after each interim analysis to decide whether the study should be terminated.

Statistical analysis

Fisher's exact test will be performed for the proportion of participants with seropositivity, and comparisons of anti-S antibody titres will be tested with the Mann-Whitney U test, and 95% CIs will be calculated. IgG concentrations below threshold of detection will be given the lowest detectable value multiplied by 0.5. A p value <0.05 will be considered statistically significant. All data will be analysed using SPSS (V.27).

Patient and public involvement

No patient involved.

Ethics and dissemination

In recent studies, no serious adverse events among transplant recipients receiving two mRNA vaccine doses were found.[12–15] Temporary reduction of immunosuppression during sepsis in kidney transplant recipients was not associated with an increased risk of rejection or long-term graft failure.[27]

This trial's results will be made available through publication. Patient data (de-identified) will be available for other researchers by request. This will be considered for researchers presenting a methodologically adequate protocol, ethical approval and signing data transfer agreement.

Study timeline

Patients will be recruited during September–November 2021, follow-up will be for 12 months. Analysis and writing of the manuscript are planned until June 2023. Current status of the study—still not recruiting.

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